Modeling and Analysis
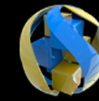# using
Stochastic Hybrid System

João Hespanha

Examples

- Biology / degradation regulation

- Biology / transcription regulation
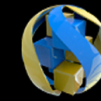
Modeling/Analysis tools

- Lyapunov-based analysis

- Moments dynamics

(ex) students: D. Antunes (IST), A. Mesquita (UCSB), Y. Xu (Advertising.com), A. Singh (UCSD)

collaborators: M. Khammash (UCSB), C. Silvestre (IST)

acknowledgements: NSF, Institute for Collaborative bio-technologies (ARO), AFOSR (STTR program)

disclaimer: This is an overview, technical details in papers referenced in bottom right corner… http://www.ece.ucsb.edu/~hespanha

Talk Outline

Examples

- Biology / degradation regulation

- Biology / transcription regulation

Modeling/Analysis tools

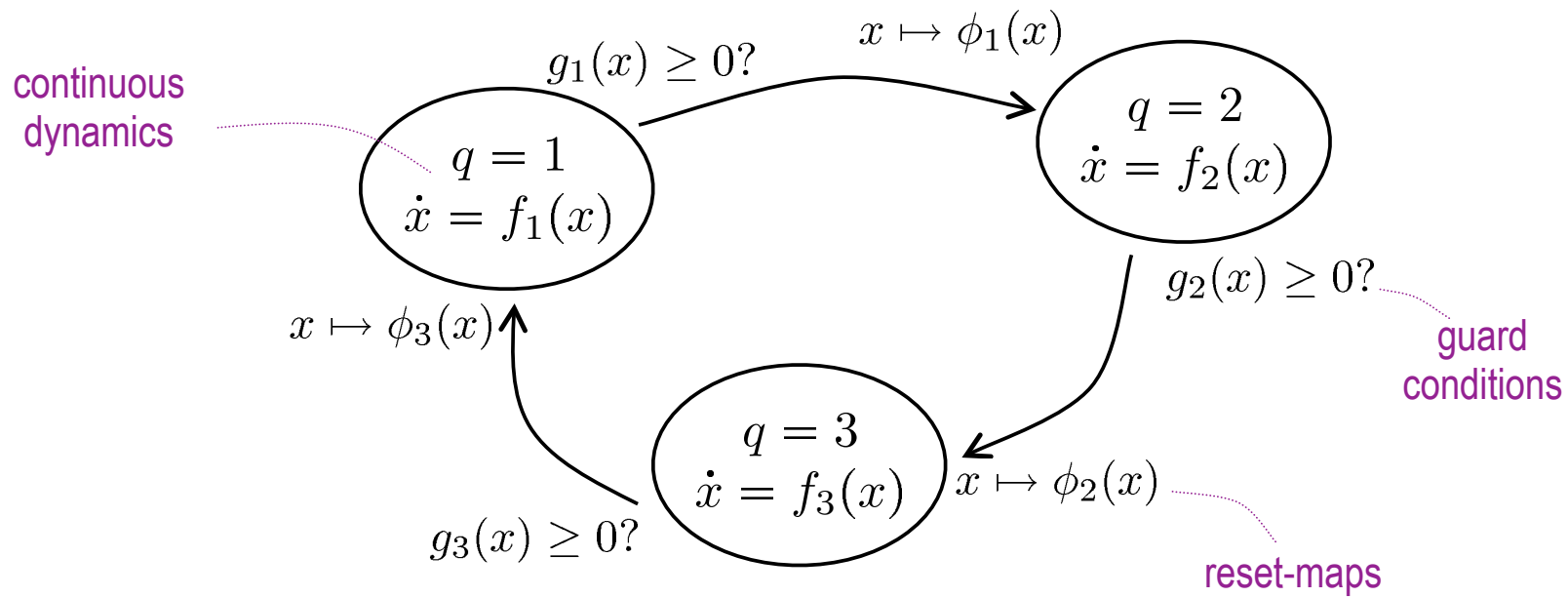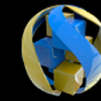- Lyapunov-based analysis

- Moments dynamics

Disclaimer:

Several other important applications/researchers not mentioned in this talk. E.g.,

- air traffic control [Bujorianu, Lygeros, Prandini, Hu, Tomlin,...]

- network traffic modeling [Bohacek, Lee, Yin, ...]

- queuing systems [Cassandras,...]

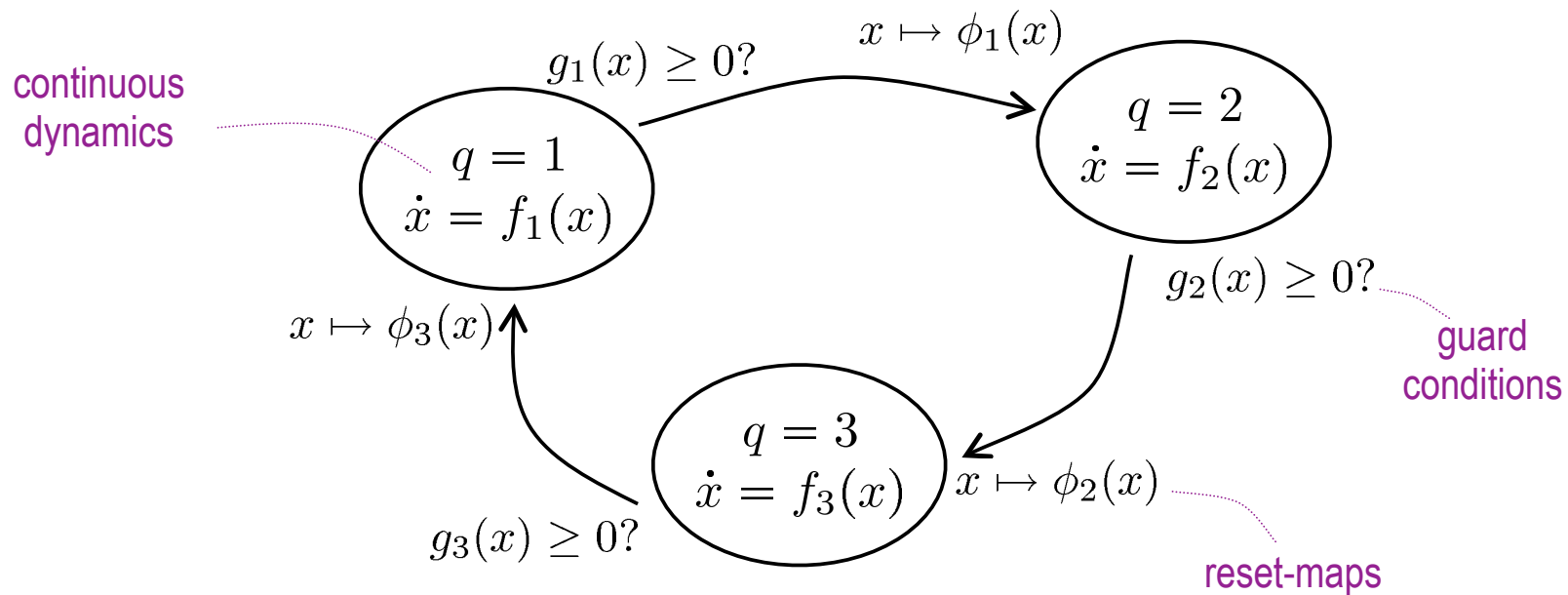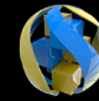- economics [Davis, Yin,…]

- biology [Hu, Julius, Lygeros, Pappas,...]

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continuous
dynamics

$x \mapsto \phi_1(x)$

$g_1(x) \geq 0?$

$q = 1$
$\dot{x} = f_1(x)$

$q = 2$
$\dot{x} = f_2(x)$

$g_2(x) \geq 0?$

guard
conditions

$x \mapsto \phi_3(x)$

$q = 3$
$\dot{x} = f_3(x)$

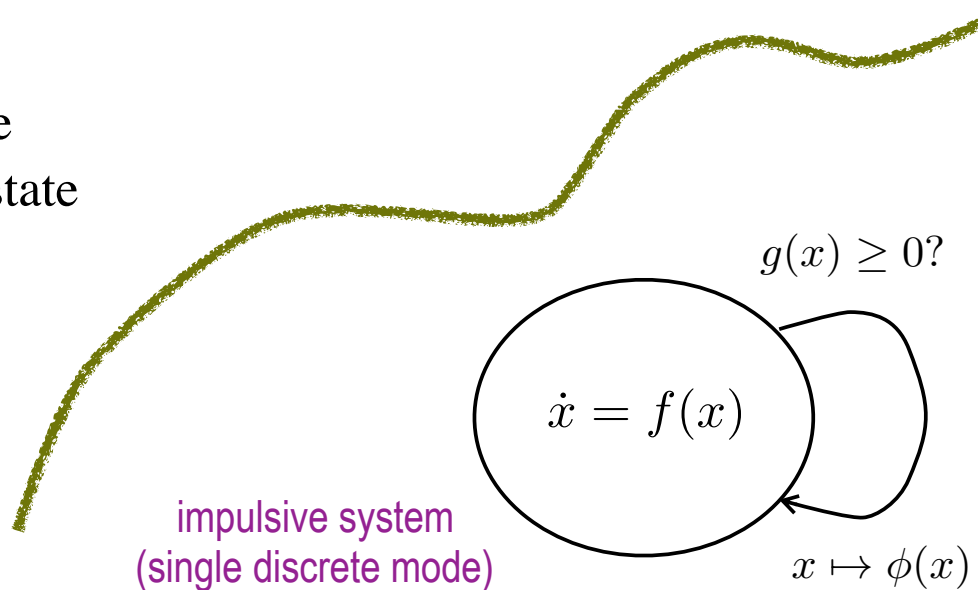$x \mapsto \phi_2(x)$

$g_3(x) \geq 0?$

reset-maps

$q(t) \in \mathcal{Q} = \{1,2,\ldots\}$ $\quad \equiv$ discrete state

$x(t) \in \mathbb{R}^n$ $\quad \equiv$ continuous state

Deterministic Hybrid Systems

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continuous dynamics

$$x \mapsto \phi_1(x)$$

$$g_1(x) \geq 0?$$

$$q = 2$$
$$\dot{x} = f_2(x)$$

$$q = 1$$
$$\dot{x} = f_1(x)$$

$$g_2(x) \geq 0?$$

$$x \mapsto \phi_3(x)$$

guard conditions

$$q = 3$$
$$\dot{x} = f_3(x)$$

$$x \mapsto \phi_2(x)$$

$$g_3(x) \geq 0?$$

reset-maps

$q(t) \in \mathcal{Q}=\{1,2,\ldots\}$ $\equiv$ discrete state
$x(t) \in \mathbb{R}^n$ $\equiv$ continuous state

$$g(x) \geq 0?$$

$$\dot{x} = f(x)$$

impulsive system
(single discrete mode)

$$x \mapsto \phi(x)$$

continuous
dynamics

$$x \mapsto \phi_1(x)$$

$$\lambda_1(x)dt$$

$$q = 1$$
$$\dot{x} = f_1(x)$$

$$q = 2$$
$$\dot{x} = f_2(x)$$

$$\lambda_2(x)dt$$

$$x \mapsto \phi_3(x)$$

$$q = 3$$
$$\dot{x} = f_3(x)$$

$$x \mapsto \phi_2(x)$$

$$\lambda_3(x)dt$$

transition intensities
(probability of transition in
small interval $(t, t+dt]$)

reset-maps
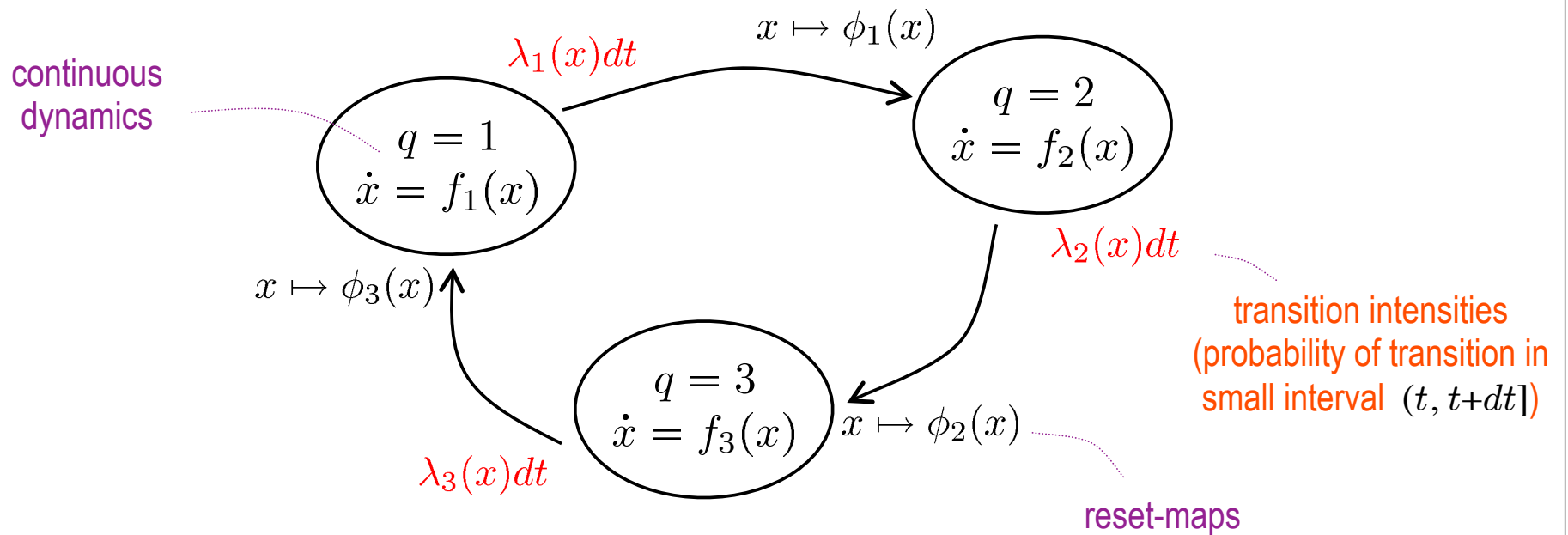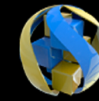
$q(t) \in \mathcal{Q} = \{1,2,\dots\}$ $\equiv$ discrete state
$x(t) \in \mathbb{R}^n$ $\equiv$ continuous state
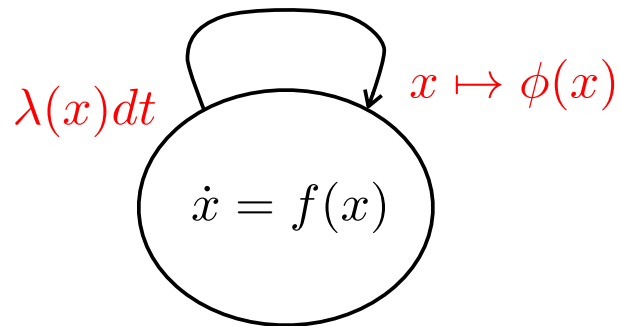
Special case:

Markovian jump system

When all λ_ℓ are constant $\Rightarrow$ time triggered SHS with exponential $t_{k+1} - t_k$

$$\lambda(x)dt \qquad x \mapsto \phi(x)$$
$$\dot{x} = f(x)$$

here we take x_0 as a given parameter

1. Initialize state:

$$x(t_0) = x_0 \quad k = 0$$

2. Draw a unit-mean exponential random variable

$$E \sim \exp(1)$$

3. Solve ODE

$$\dot{x} = f(x) \quad x(t_k) = x_k \quad t \geq t_k$$

until time t_{k+1} for which

$$\int_{t_k}^{t_{k+1}} \lambda(x(t))dt \geq E$$

4. Apply the corresponding reset map

$$x(t_{k+1}) = x_{k+1} := \phi(x^-(t_{k+1}))$$

set $k = k + 1$ and go to 2.

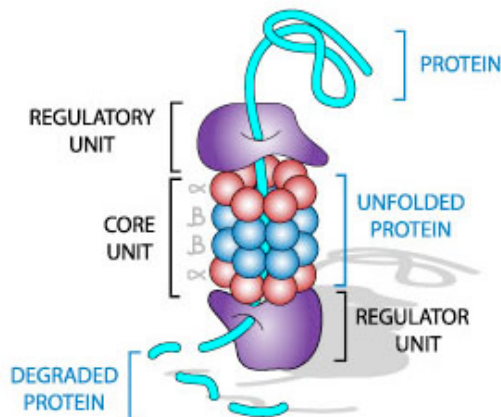$x(t)$ = concentration of protein X at time t

$$\dot{x} = k - dx \qquad\qquad x \xrightarrow{exp} \frac{k}{d}$$

production of X at
constant rate

degradation of
"each protein X"
at a constant rate

Degradation regulation $\equiv$ feedback mechanism used to regulate the concentration
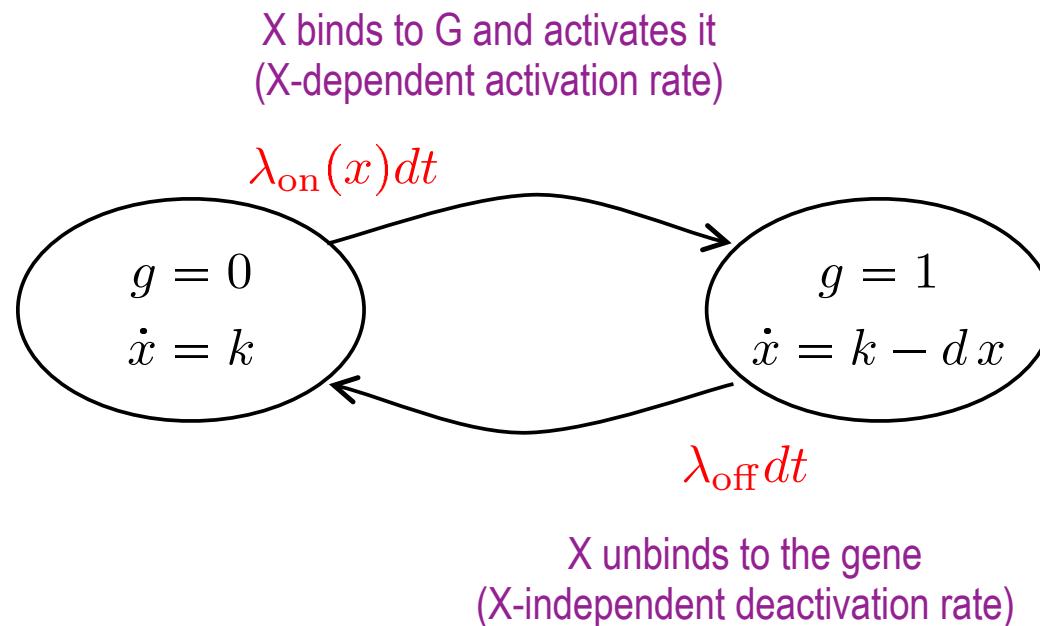of a protein by destroying protein molecules "in excess"

$x(t)$ = concentration of protein X at time t

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production of X at
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degradation of
"each protein X"
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Degradation regulation $\equiv$ feedback mechanism used to regulate the concentration
of a protein by destroying protein molecules "in excess"

PROTEIN

REGULATORY
UNIT

CORE
UNIT

UNFOLDED
PROTEIN

REGULATOR
UNIT

DEGRADED
PROTEIN

angiebiotech.com

Suppose: Gene G produces an enzyme that
tags proteins for destruction
(e.g., ubiquitination for subsequent
degradation by the proteasome)

$$\begin{cases} \dot{x} = k & \text{G off} \\ \dot{x} = k - d\,x & \text{G on} \end{cases}$$

protein is only
degraded when the
Gene is on

Negative feedback $\equiv$ when the protein X is a transcription factor that activates the gene

X binds to G and activates it
(X-dependent activation rate)

$\lambda_{\mathrm{on}}(x)dt$

$g = 0$
$\dot{x} = k$

$g = 1$
$\dot{x} = k - d\,x$

$\lambda_{\mathrm{off}}dt$
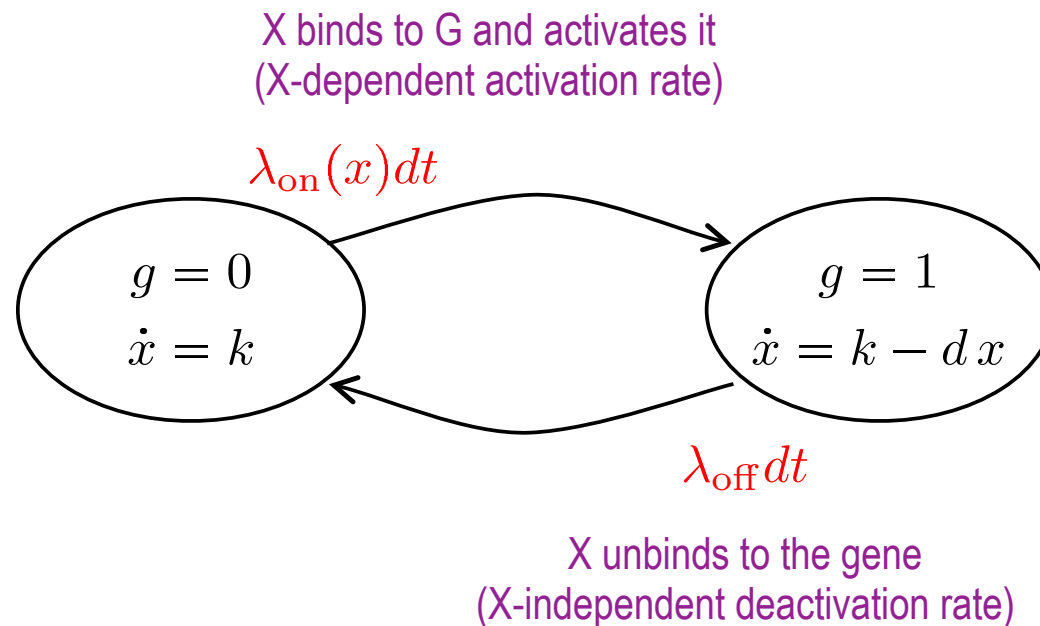
X unbinds to the gene
(X-independent deactivation rate)

Is this enough to keep the variance bounded? Small?

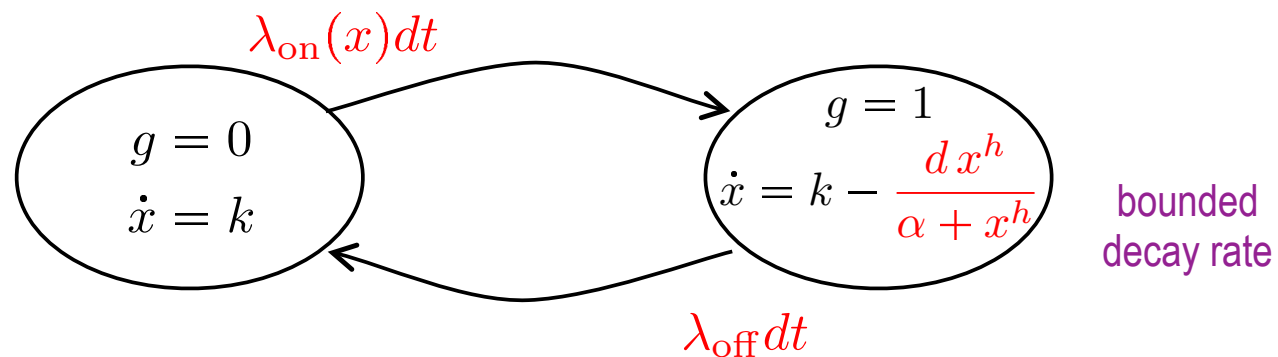*For which gene activation rates $\lambda_{\mathrm{on}}(x)$?*

What about higher order moments?

Negative feedback ≡ when the protein X is a transcription factor that activates the gene

X binds to G and activates it
(X-dependent activation rate)

$\lambda_{\mathrm{on}}(x)dt$

$g = 0$
$\dot{x} = k$

$g = 1$
$\dot{x} = k - d\,x$

$\lambda_{\mathrm{off}}\,dt$

X unbinds to the gene
(X-independent deactivation rate)

What if the degradation is constrained by the enzyme concentration?

$\lambda_{\mathrm{on}}(x)dt$

$g = 0$
$\dot{x} = k$

$g = 1$
$\dot{x} = k - \dfrac{d\,x^h}{\alpha + x^h}$

bounded
decay rate

$\lambda_{\mathrm{off}}\,dt$

$$\dot{x} = f(x) \qquad x \in \mathbb{R}^n$$

Given scalar-valued function $V : \mathbb{R}^n \to \mathbb{R}$

$$\frac{dV(x(t))}{dt} = \frac{\partial V(x(t))}{\partial x} f(x(t))$$

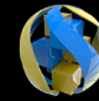derivative
along solution
to ODE

$L_f V$
Lie derivative of V

Basis of "Lyapunov" formal arguments to establish boundedness and stability…

E.g., picking $V(x) := \|x\|^2$

$$\frac{dV(x(t))}{dt} = \frac{\partial V}{\partial x} f(x) \leqslant 0 \quad \Rightarrow \quad V(x(t)) = \|x(t)\|^2 \leqslant \|x(0)\|^2$$

$\|x\|^2$ remains bounded along trajectories !

$$\lambda_\ell(q,x)dt \qquad (q,x) \mapsto \phi_\ell(q,x)$$
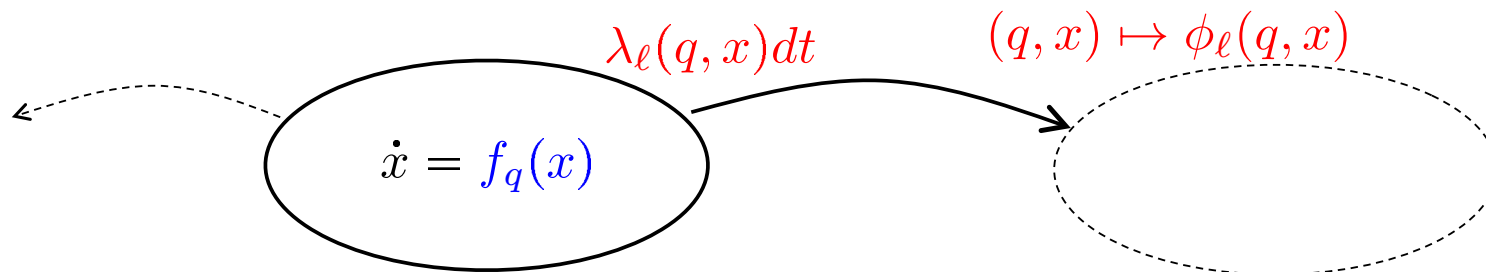
$$\dot{x} = f_q(x)$$

Given scalar-valued function $V : \mathcal{Q} \times \mathbb{R}^n \to \mathbb{R}$

x & q are discontinuous, but the expected value is differentiable

$$\frac{d}{dt} \mathrm{E}\Big[V\big(q(t), x(t)\big)\Big] = E\Big[(LV)\big(q(t), x(t)\big)\Big]$$

Dynkin's formula
(in differential form)

where

$$(LV)(q,x) := \frac{\partial V}{\partial x}(q,x) f_q(x) \quad \text{......... Lie derivative}$$

instantaneous variation

(extended) generator of the SHS

$$+ \sum_{\ell=1}^{m} \lambda_\ell(q,x)\Big(V\big(\phi_\ell(q,x)\big) - V(q,x)\Big) \quad \text{......... Reset term}$$

intensity
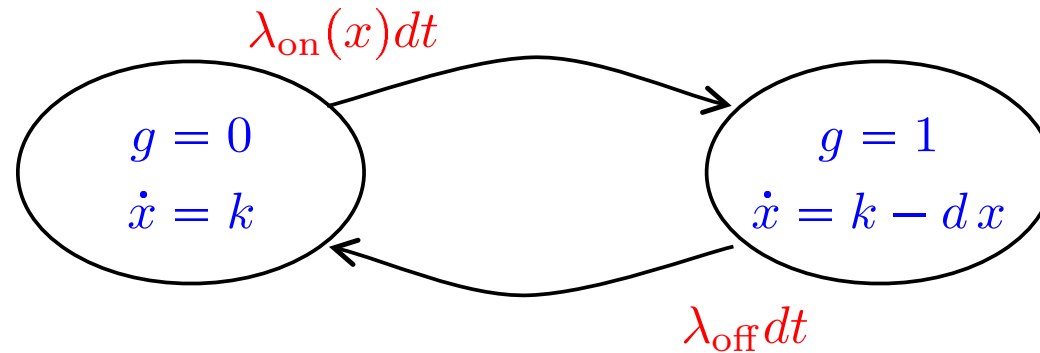
$$(LV)(g,x) = \frac{\partial V(g,x)}{\partial x}(k - gd) + \big(\lambda_{\mathrm{on}}(x)(1-g) - \lambda_{\mathrm{off}}g\big)\big(V(1,x) - V(0,x)\big)$$

$$\dot{x} = f(x) + g(x)\dot{w}$$

$$\lambda(x)dt$$

$$x \mapsto \phi(x)$$

$$\frac{d}{dt}\,\mathrm{E}\Big[V\big(x(t)\big)\Big] = E\Big[(LV)\big(x(t)\big)\Big]$$
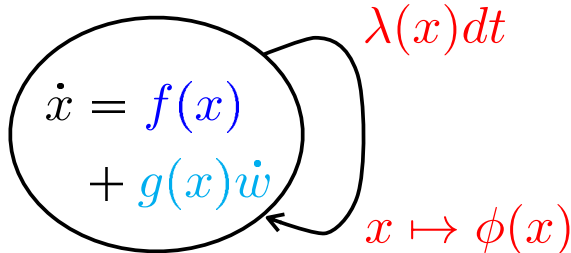
sample-path notions

class-K functions:
(zero at zero & mon. increasing)

$$\begin{cases} \alpha_1(\|x\|) \le V(x) \le \alpha_2(\|x\|) \\ LV(x) \le -\alpha_3(\|x\|) \end{cases}$$

$\Rightarrow$

probability of $\|x(t)\|$ exceeding any given bound M, can be made arbitrarily small by making $\|x_0\|$ small

$$\begin{cases} \mathrm{P}\left(\exists t : \|x(t)\| \ge M\right) \le \dfrac{\alpha_2(\|x_0\|)}{\alpha_1(M)} \\ \mathrm{P}\left(x(t) \to 0\right) = 1 \end{cases}$$

almost sure (a.s.)
asymptotic stability

expected-value notions

$$\begin{cases} V(x) \ge 0 \\ LV(x) \le -W(x) \end{cases}$$

$\Rightarrow$

$$\int_0^\infty \mathrm{E}\Big[W\big(x(t)\big)\Big]dt < \infty$$

stochastic stability
(mean square when $W(x) = \|x\|^2$)

$$\begin{cases} V(x) \ge W(x) \ge 0 \\ LV(x) \le -\mu V + c \end{cases}$$

$\Rightarrow$

$$\mathrm{E}\Big[W\big(x(t)\big)\Big] \le e^{-\mu t}V(x_0) + \frac{c}{\mu}$$

exponential stability
(mean square when $W(x) = \|x\|^2$)

$$\lambda_{\mathrm{on}}(x)dt$$

$$
\begin{array}{c}
g = 0 \\
\dot{x} = k
\end{array}
\qquad
\begin{array}{c}
g = 1 \\
\dot{x} = k - d\,x
\end{array}
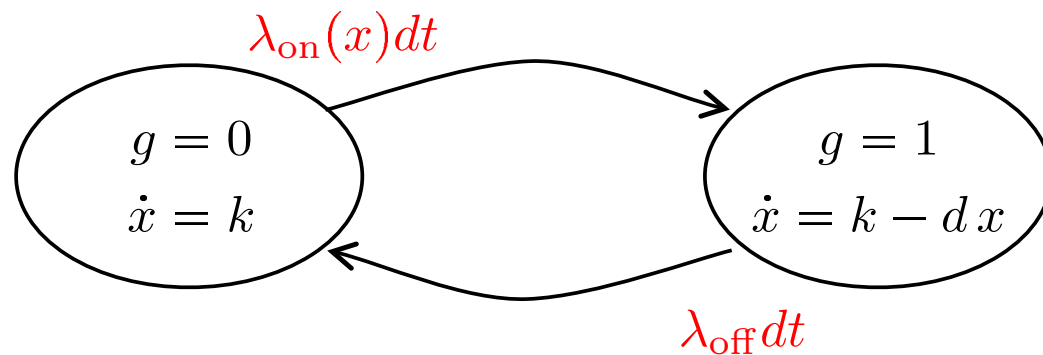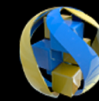$$

$$\lambda_{\mathrm{off}}\,dt$$
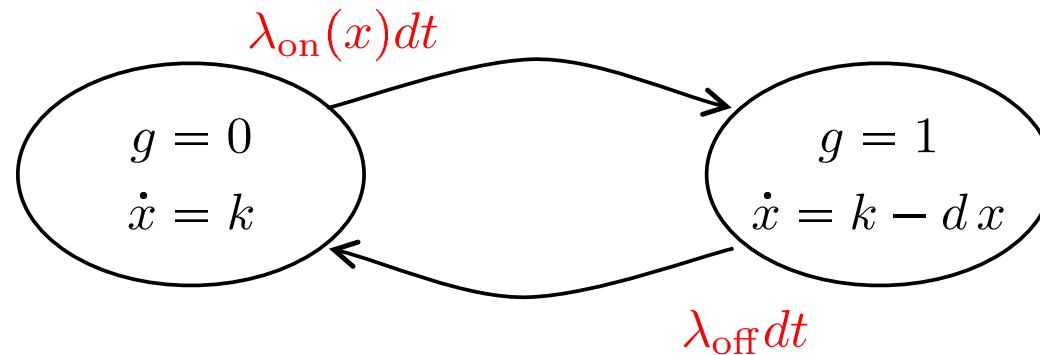
Assume $\lambda_{\mathrm{on}}(x) \geqslant \epsilon > 0$: For every $m \geqslant 1$, $\exists\, p_0, p_1, \mu, c > 0$ such that

$$
\begin{cases}
V(g,x) = p_g x^m \\
(LV)(g,x) \leqslant -\mu V(x) + c
\end{cases}
\quad \Rightarrow \quad
\mathrm{E}\!\left[x(t)^m\right] \leqslant e^{-\mu t} x(0)^m + \frac{c}{\mu}
$$

all moments are bounded

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$\lambda_{\text{on}}(x)dt$

$$g = 0$$
$$\dot{x} = k$$

$$g = 1$$
$$\dot{x} = k - d\,x$$

$\lambda_{\text{off}}dt$

$$\mathrm{E}\left[x(t)^m\right] \leqslant e^{-\mu t}x(0)^m + \frac{c}{\mu}$$

all moments are bounded

$\lambda_{\text{on}}(x)dt$

$$g = 0$$
$$\dot{x} = k$$

$$g = 1$$
$$\dot{x} = k - \frac{d\,x^h}{\alpha + x^h}$$

bounded
decay rate

$\lambda_{\text{off}}dt$
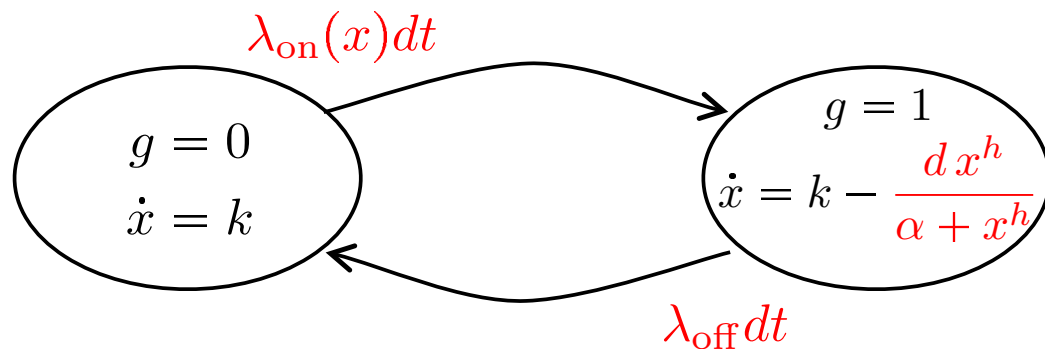
Assume λ_{on} radially unbounded: For every $m \geqslant 1, \exists p_0, p_1, \mu, c > 0$ such that

$$\begin{cases} V(g,x) = x^{m+1} + p_g x^m \\ (LV)(g,x) \leqslant -\mu x^m + c \end{cases} \Rightarrow \quad \frac{1}{T}\int_0^T \mathrm{E}[x(t)^m]dt \leqslant c + \frac{V(g(0), x(0))]}{T}, \ \forall T$$

Examples

- Biology / degradation regulation

- Biology / transcription regulation

Modeling/Analysis tools

- Lyapunov-based analysis

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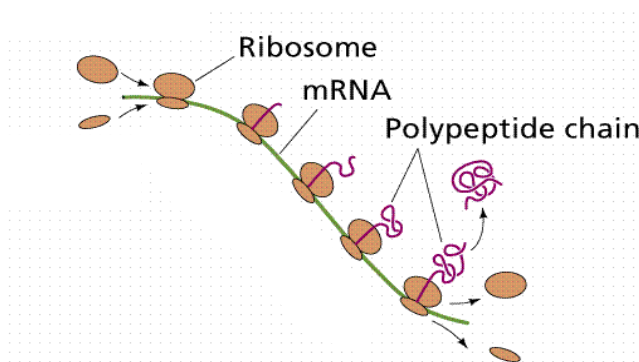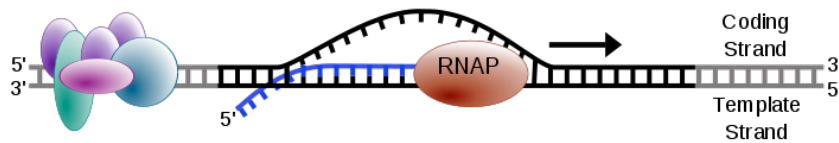
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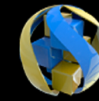
Gene expression ≡ process by which a gene (encoded in the DNA) produces proteins:
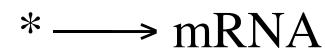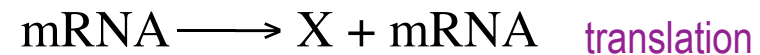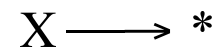
http://en.wikipedia.org

Coding Strand

RNAP

5'
3'
5'

3'
5'

Template Strand

Ribosome

mRNA

Polypeptide chain

$* \longrightarrow mRNA$ transcription (constant rate)

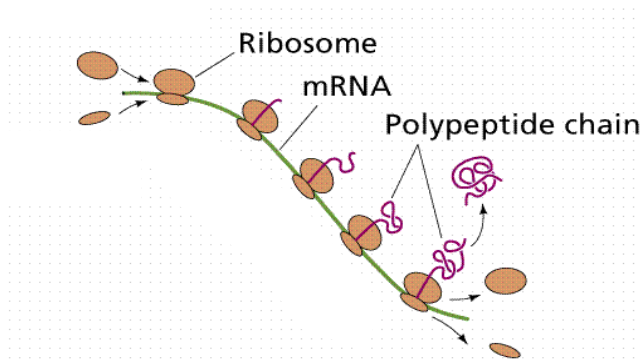$mRNA \longrightarrow X + mRNA$ translation

$mRNA \longrightarrow *$ mRNA decay

$X \longrightarrow *$ protein decay

one transcription event

http://en.wikipedia.org

Coding Strand

RNAP

5'
3'

3'
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Template Strand

5'

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Polypeptide chain

$* \longrightarrow \text{mRNA}$ transcription (constant rate)

$\text{mRNA} \longrightarrow \text{X} + \text{mRNA}$ translation

$\text{mRNA} \longrightarrow *$ mRNA decay

one transcription event
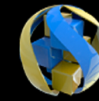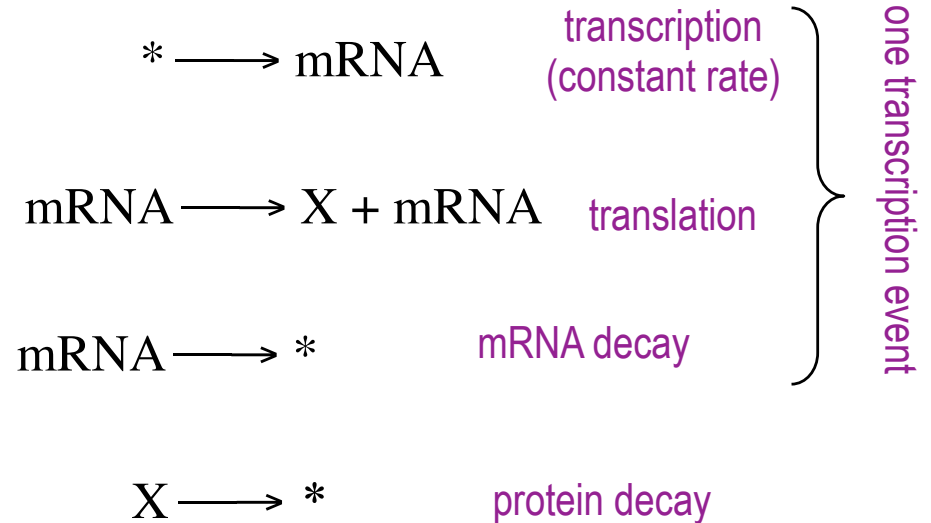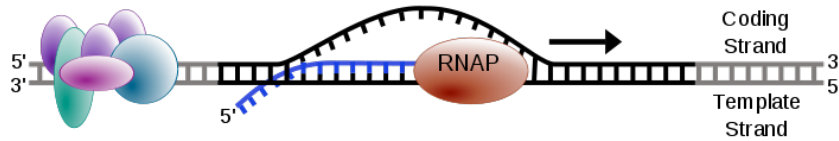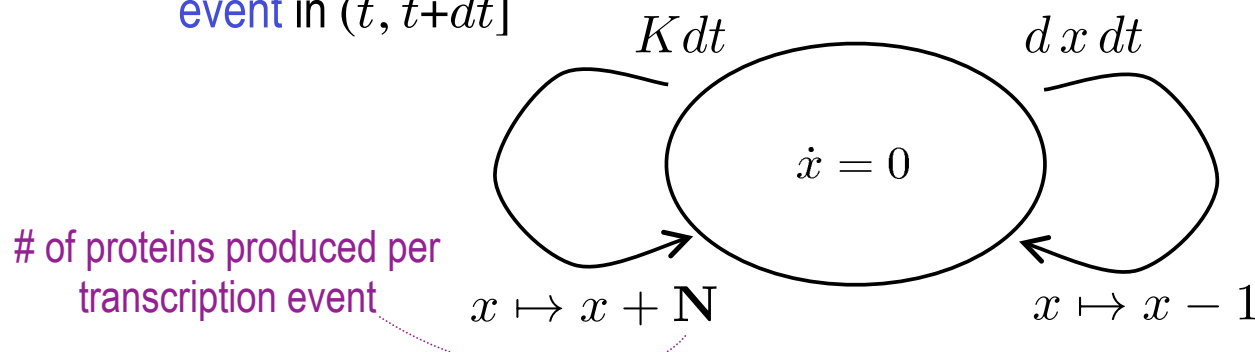
$\text{X} \longrightarrow *$ protein decay

$x(t) \equiv$ number of proteins at time t

prob. of one transcription event in $(t, t+dt]$

prob. of one decay event in $(t, t+dt]$

$K \, dt$
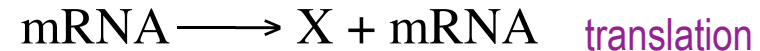
$d \, x \, dt$

$\dot{x} = 0$

# of proteins produced per transcription event

$x \mapsto x + \mathbf{N}$

$x \mapsto x - 1$

equivalent to Gillespie's stochastic simulation algorithm (SSA)

http://en.wikipedia.org

Coding
Strand

RNAP

Template
Strand

Ribosome

mRNA

Polypeptide chain

$* \longrightarrow$ mRNA

transcription
(constant rate)

mRNA $\longrightarrow$ X + mRNA   translation
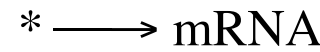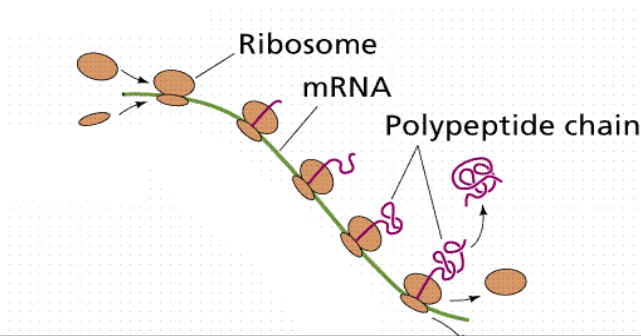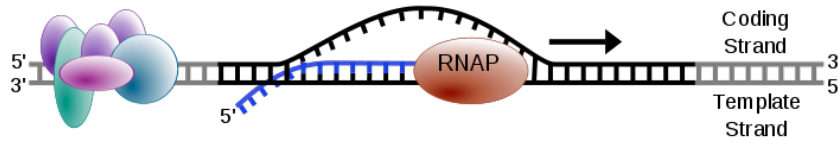
mRNA $\longrightarrow *$ mRNA decay
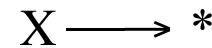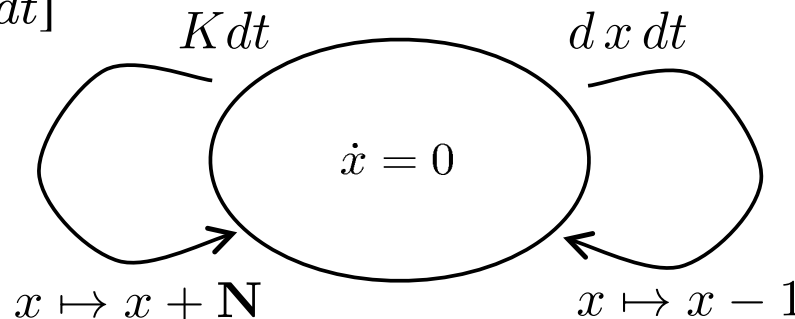
X $\longrightarrow *$ protein decay

one transcription event

*How to go beyond stability/bounds and
study the dynamics of means, variances, co-variances, etc.?*

prob. of one transcription
event in $(t, t+dt]$

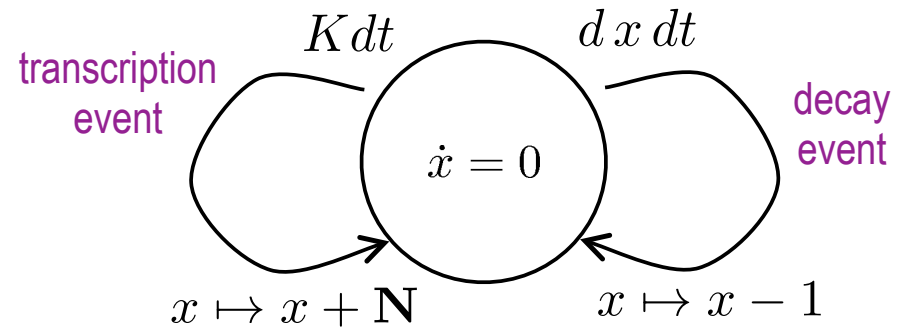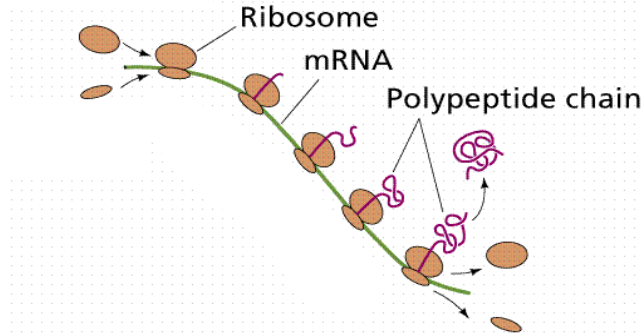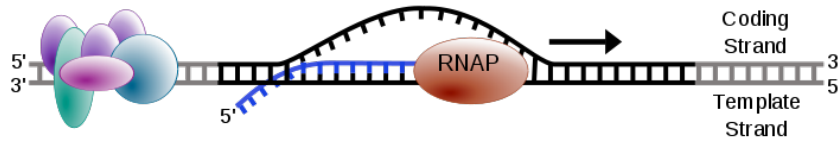prob. of one decay
event in $(t, t+dt]$

$K\,dt$ $d\,x\,dt$

$\dot{x} = 0$

# of proteins produced per
transcription event

$x \mapsto x + \mathbf{N}$ $x \mapsto x - 1$

equivalent to Gillespie's
stochastic simulation
algorithm (SSA)

Moment Dynamics

http://en.wikipedia.org

Coding Strand

RNAP

Template Strand

Ribosome
mRNA
Polypeptide chain

$K\,dt$ transcription event

$d\,x\,dt$ decay event

$\dot{x} = 0$

$x \mapsto x + \mathbf{N}$

$x \mapsto x - 1$

$$\frac{d}{dt}\,\mathrm{E}\big[V(x)\big] = E\big[(LV)(x)\big]$$

$$(LV)(x) = K\Big(V(x+\mathbf{N}) - V(x)\Big)$$
$$+ \, d\,x\Big(V(x-1) - V(x)\Big)$$

$$\frac{dE[x]}{dt} = K\,\mathrm{E}[\mathbf{N}] - d\,\mathrm{E}[x]$$

$$\frac{dE[x^2]}{dt} = K\,\mathrm{E}[\mathbf{N}^2] + (2K\,\mathrm{E}[\mathbf{N}] + d)\mathrm{E}[x] - 2d\,\mathrm{E}[x^2]$$

One can show that $\mathrm{E}[\mathbf{N}] = N := \dfrac{\text{mRNA translation rate}}{\text{mRNA decay rate}}$ $\mathrm{Var}[\mathbf{N}] = N^2 - N$

http://en.wikipedia.org

5'
3'

RNAP

Coding
Strand

3'
5'

Template
Strand

5'

Ribosome

mRNA

Polypeptide chain

transcription
event

$K\,dt$

$d\,x\,dt$

$\dot{x} = 0$

decay
event

$x \mapsto x + \mathbf{N}$

$x \mapsto x - 1$
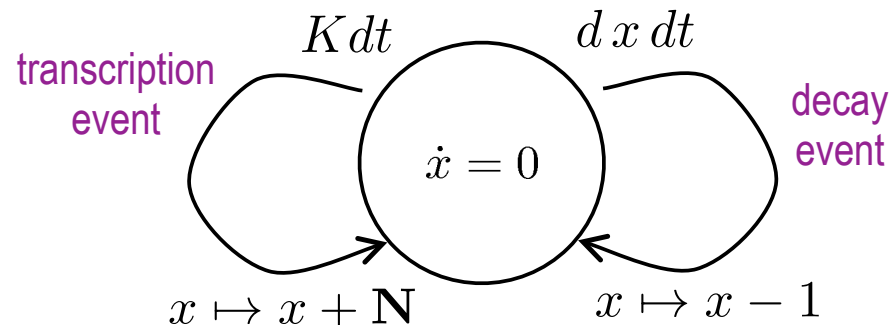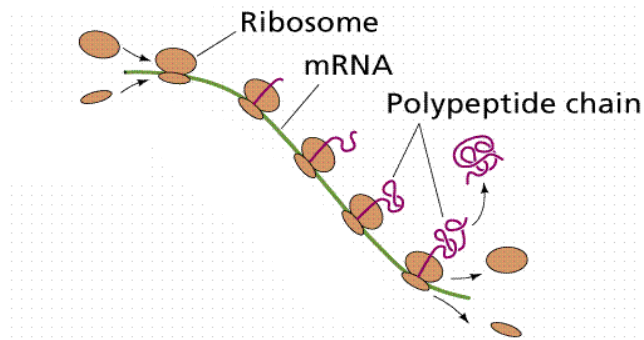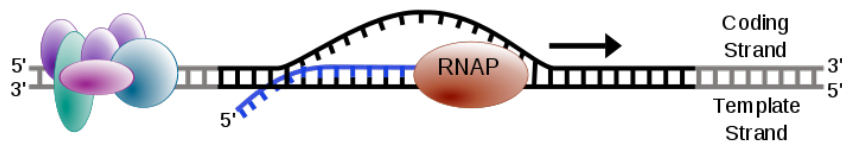
Thus, at steady-state,

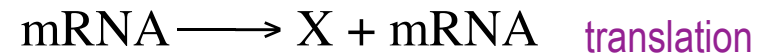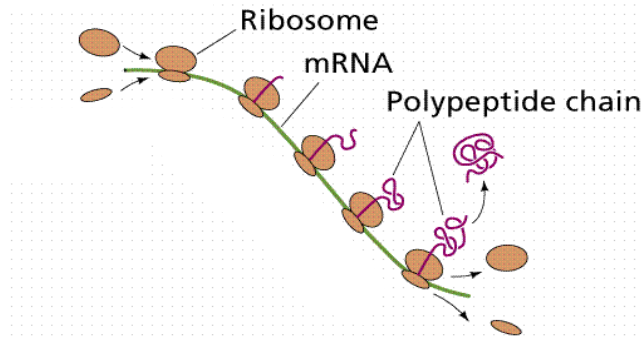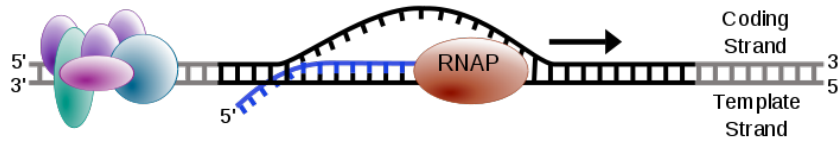$$\mathrm{E}[x] = \frac{KN}{d}$$

$$\mathrm{CV}[x] = \frac{\mathrm{StdDev}[x]}{\mathrm{E}[x]} = \sqrt{\frac{d}{K}} = \sqrt{\frac{N}{\mathrm{E}[x]}}$$

- measure of stochastic fluctuations in protein level x (normalized by mean population)
- **intrinsic noise** (solely due to random protein expression/degradation)

$$N := \frac{\mathrm{mRNA\ translation\ rate}}{\mathrm{mRNA\ decay\ rate}}$$

Auto-Regulated Gene Expression

http://en.wikipedia.org

$$* \longrightarrow \text{mRNA}$$

transcription
(**non-constant** rate)

$$\text{mRNA} \longrightarrow X + \text{mRNA}$$

translation

$$\text{mRNA} \longrightarrow *$$

mRNA decay

$$X \longrightarrow *$$

protein decay
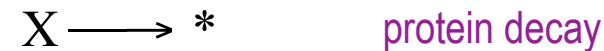
Protein production rate is a function of the current protein molecule count through *transcription regulation*:

transcriptional response
(stochastic rate at which
transcription events occur)

$$g(x)\, dt \qquad\qquad d\, x\, dt$$

$$\dot{x} = 0$$

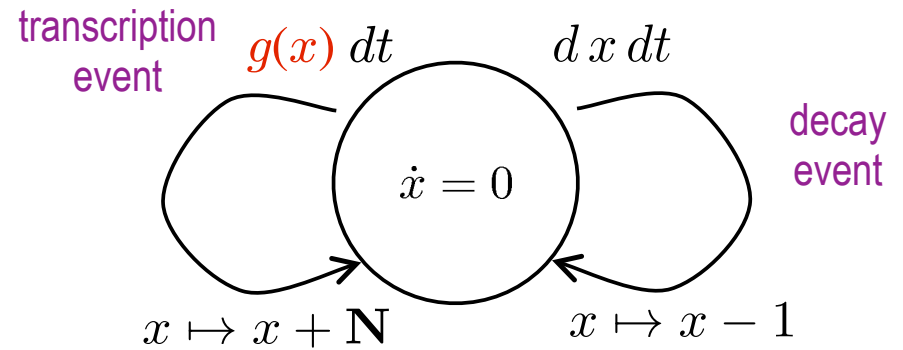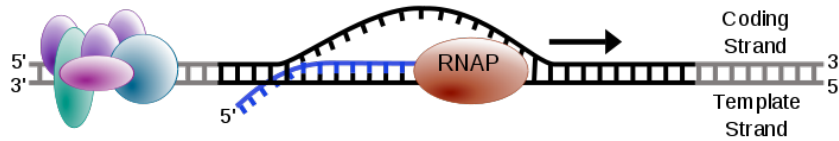$$x \mapsto x + \mathbf{N} \qquad\qquad x \mapsto x - 1$$
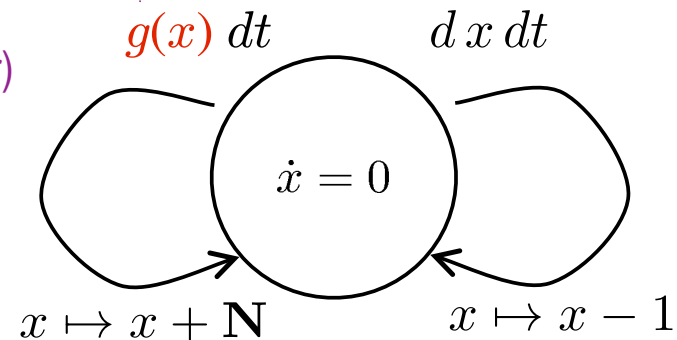
- Altering the RNA polymerase specificity for a given promoter or set of promoters
- Binding to non-coding sequences on the DNA to impede RNA polymerase's progress
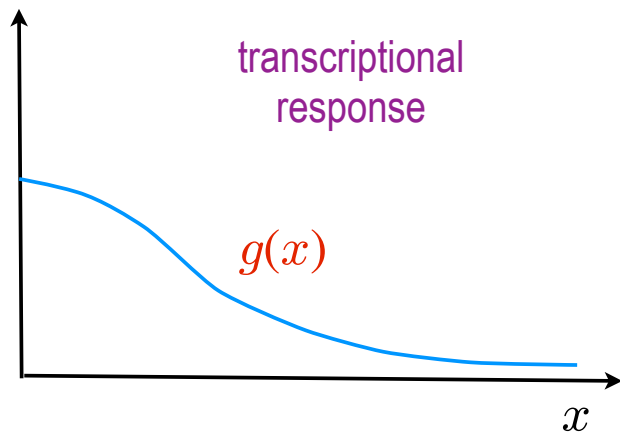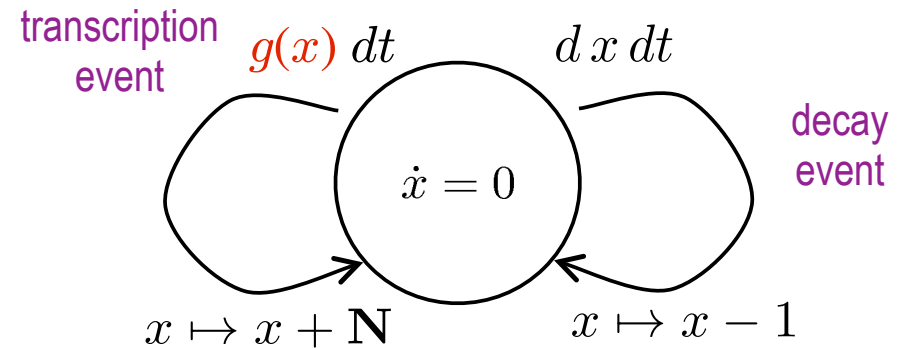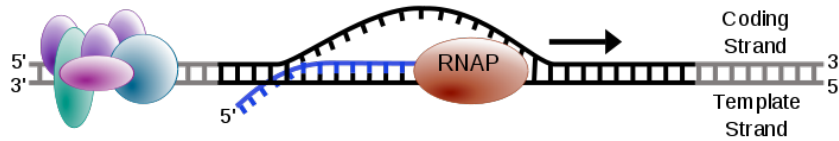
Auto-Regulatory Negative Feedback

http://en.wikipedia.org

Coding Strand

RNAP

Template Strand

transcription event $\qquad g(x)\, dt$ $\qquad d\, x\, dt$

decay event

$$\dot{x} = 0$$

$$x \mapsto x + \mathbf{N} \qquad x \mapsto x - 1$$

negative feedback ≡ protein production rate is a **decreasing** function of the protein molecule count

transcriptional response

$g(x)$

x

- Common form of auto regulation (e.g., half of the repressors in *E. Coli*)
- Experimentally shown to exhibit noise reduction ability

Moment Dynamics

http://en.wikipedia.org

transcription event $\quad g(x)\,dt \quad\quad d\,x\,dt$

$\dot{x} = 0$

decay event

$x \mapsto x + \mathbf{N} \quad\quad x \mapsto x - 1$

$$\frac{d}{dt}\,\mathrm{E}\big[V(x)\big] = E\big[(LV)(x)\big]$$

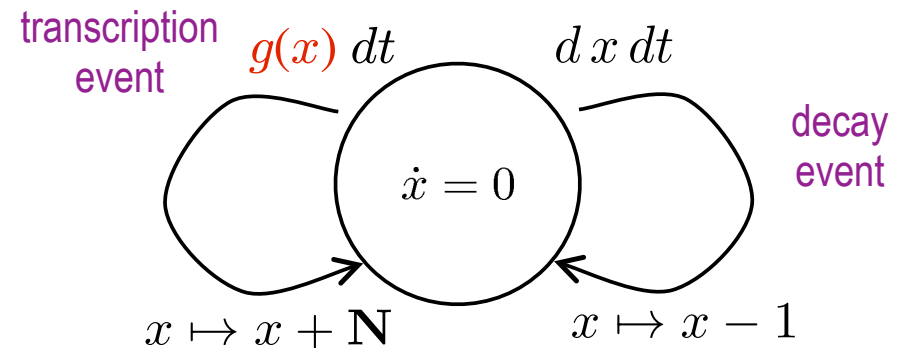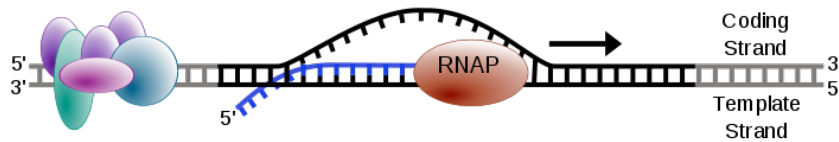$$(LV)(x) = g(x)\Big(V(x+\mathbf{N}) - V(x)\Big)$$
$$+ \, d\,x\Big(V(x-1) - V(x)\Big)$$

$$\frac{dE[x]}{dt} = \mathrm{E}[\mathbf{N}]\mathrm{E}[g(x)] - d\,\mathrm{E}[x]$$

$$\frac{dE[x^2]}{dt} = \mathrm{E}[\mathbf{N}^2]\mathrm{E}[g(x)] + 2\,\mathrm{E}[\mathbf{N}]\mathrm{E}[g(x)x] + d\mathrm{E}[x] - 2d\,\mathrm{E}[x^2]$$

- When $g(x)$ is an affine function we still get a finite system of linear equations
- When $g(x)$ is a polynomial, we get a closed but infinite system of linear equation (general property of polynomial SHSs)
- For other $g(x)$, one generally does not get a closed system of equations
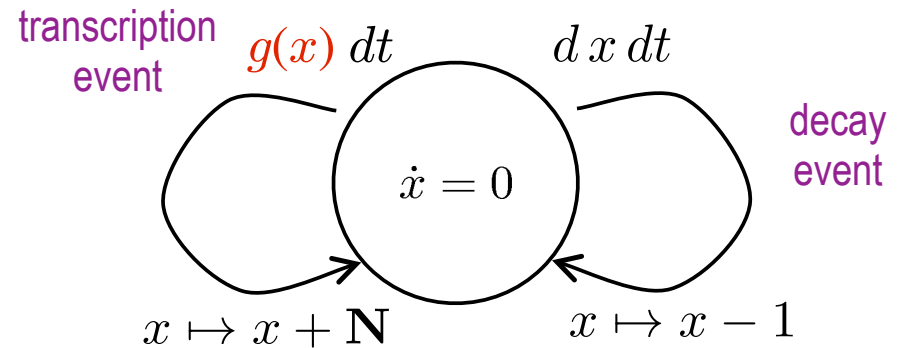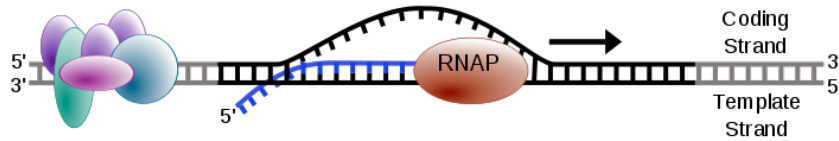
Auto-Regulated Gene Expression

http://en.wikipedia.org

Coding
Strand

RNAP

Template
Strand

transcription
event

$g(x)\,dt$

$d\,x\,dt$

$\dot{x} = 0$

decay
event

$x \mapsto x + \mathbf{N}$

$x \mapsto x - 1$

Approximate Analysis Methods

- Distribution-based: assume a specific type of distribution (Normal, LogNormal, Poisson, etc.) and force dynamics to be compatible with this type of distribution

- Large numbers/large volume: take the limit as volume $\rightarrow \infty$ and assume concentrations do not $\rightarrow 0$

- Derivative matching: force solutions of approximate dynamics to match exact equation locally in time

- Linearization: Linearize transcriptional response around steady-state value of the mean

Auto-Regulatory Negative Feedback

http://en.wikipedia.org

Coding Strand
RNAP
Template Strand

transcription event $\quad g(x)\,dt \qquad d\,x\,dt \quad$ decay event

$$\dot{x} = 0$$

$$x \mapsto x + \mathbf{N} \qquad\qquad x \mapsto x - 1$$

For a transcriptional response approximately linear around steady-state mean

$$g(x) \approx g(x^*) + g'(x^*)(x - x^*)$$

steady-state population mean
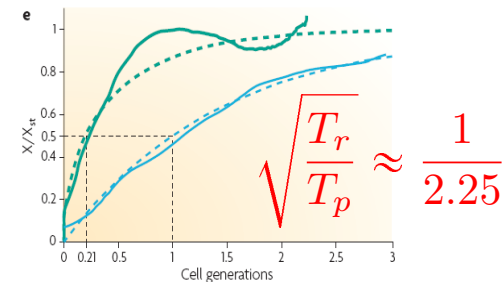
protein's response-time (with feedback)

$$CV[x] = \frac{\text{StdDev}[x]}{\text{E}[x]} = \sqrt{\frac{T_r}{T_p}\frac{N}{\text{E}[x]}}$$

"unregulated" intrinsic noise
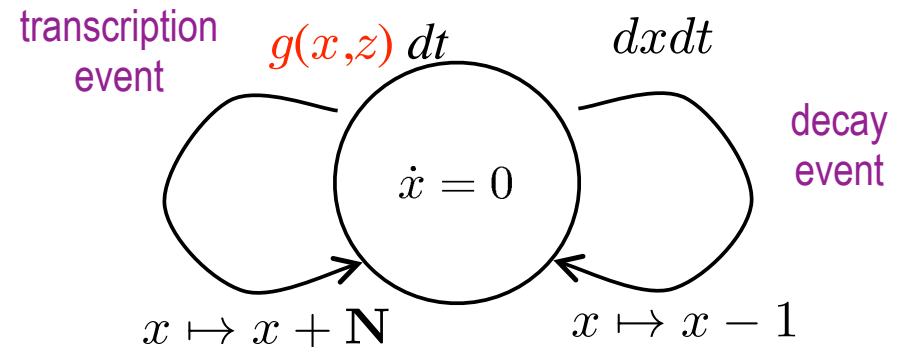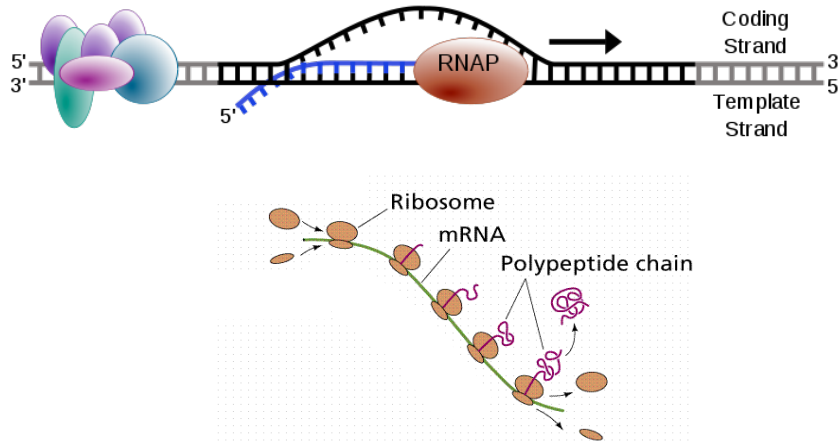
protein's half-live (response time without feedback)

$$\sqrt{\frac{T_r}{T_p}} \approx \frac{1}{2.25}$$

experimental study using a synthetic gene circuit in which the repressor TetR fused to GFP represses its own promoter

Negative feedback reduces T_r with respect to $T_p \Rightarrow$ decreases noise

Rosenfeld et al, J. Molecular Biology, 2002

http://en.wikipedia.org

transcription event

$g(x,z)\ dt$

$dxdt$

decay event

$\dot{x} = 0$

$x \mapsto x + \mathbf{N}$

$x \mapsto x - 1$

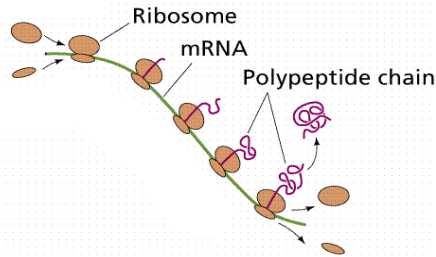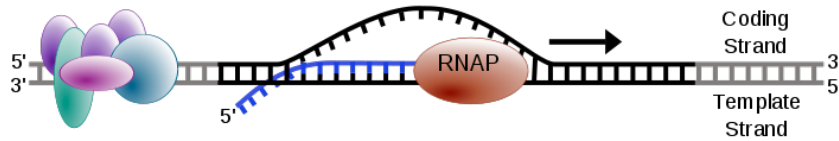In practice, transcription rate also depends on exogenous species (e.g., RNA polymerase and other enzymes)

$g(x, z) \equiv$ transcriptional response (stochastic rate at which transcription events occur)

exogenous species (with stochastic fluctuations)

http://en.wikipedia.org
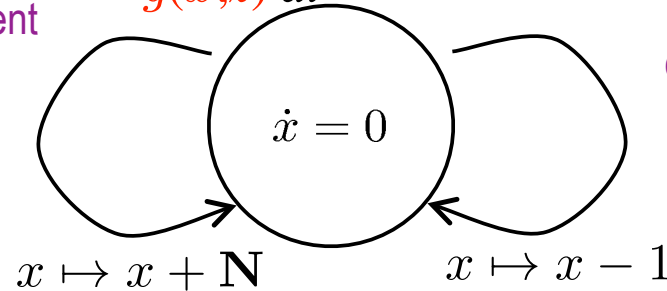
transcription event $g(x,z)\,dt$ $dxdt$

decay event

$\dot{x} = 0$

$x \mapsto x + \mathbf{N}$ $x \mapsto x - 1$

CV of extrinsic species

$$CV[x]^2 \approx \underbrace{\frac{T_r}{T_p}\frac{N}{E[x]}}_{\substack{\text{intrinsic noise} \\ \text{(as before)}}} + \underbrace{\left(\frac{T_r}{T_p}\right)^2 CV[z]^2}_{\text{extrinsic noise}}$$
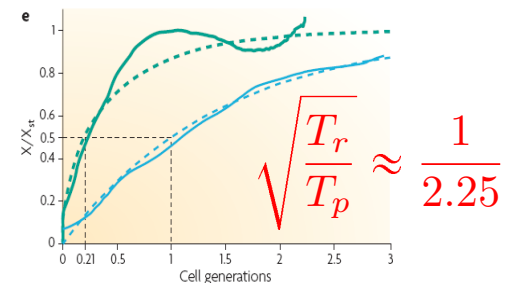
$T_r \equiv$ protein's response-time (with feedback)

$T_p \equiv$ protein's half-live (response time without feedback)

Negative feedback reduces T_r with respect to T_p

- attenuates both intrinsic and extrinsic noise
- more efficient at reducing extrinsic noise
- surprisingly good matches with experimental results…
- offers a new technique to discover sources of extrinsic noise (solve for $CV[z]$!)

$$\sqrt{\frac{T_r}{T_p}} \approx \frac{1}{2.25}$$

[Singh *et al*, 2009; related results by Paulsson 2004]

UC SANTA BARBARA
engineering

1. SHS models that find use in several areas
   (network traffic modeling, networked control systems, distributed estimation, biochemistry, population dynamics in ecosystems)

2. The analysis of SHSs is challenging but there are tools available
   (stability conditions for linear time-triggered SHS, Lyapunov methods, moment dynamics, linearization, truncations)

3. Lots of work to be done …